CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-106

Approvable Letter (S)

peptides were assigned molecular weights of 403.44 and 761.79, respectively. The molecular weights of these peptides are greater than that of the T3 fragment (M.W. of 360.37), which was successfully resolved.

h. Clarify why peptide T3 is not present in the chromatogram of B2036-PEG since T3 is unaffected by pegylation.

i. Submit characterization data for [redacted] Data should include N- and C-terminal sequencing, mass spectrometry analysis, and identification of the deamidated residues.

3. Bioassay:

a. Submit the specifications for the cell line, including tests for relevant phenotypic and genotypic markers.

b. Describe the preparation and characterization of the master and working cell banks for the FDC-P1 cell line.

c. Describe how the cell is activated in the presence of human growth hormone.

d. The written procedure for the Growth Hormone Antagonist (GHA) bioassay includes acceptance criteria that are not supported by the method validation. Revise the following in the procedure:

i) The acceptance criteria mean reference IC50 for the formulated bulk should be 70 - 80% for the bulk intermediate and 90 - 110% for the drug product;

ii) The mean bioactivity acceptance criteria from six plates must have a % CV of ≤ 20%; and

iii) Interwell reproducibility acceptance criteria should be ≤ 15%.

e. Provide supporting evidence that the *Mycoplasma* are not destroyed when the FDC-P1 samples are frozen at –70°C before being shipped to the testing laboratory for *Mycoplasma* testing.

4. Detailed Description of the Process:

a. Submit results of the characterization of the production strain for phenotypic and genotypic markers, including those that will be periodically monitored to ensure identity and purity of the culture.

b. Submission of a U.S. patent is not appropriate for the description of the gene construction of B2036. Submit a narrative of the gene construction.

c. Submit a detailed description of the filtration and filling process of the bulk intermediate.

d. Describe the criteria for pooling the B2036-PEG fractions after the [redacted]

e. Verify that the [redacted] Amino is of bovine origin.

5. Regarding production and process control:
   a. Implement in-process controls with acceptance criteria for process- and product-related substances and impurities at appropriate steps in the manufacturing process.
   b. Implement in-process controls with acceptance criteria for critical parameters during processing (e.g., clarity to detect phase cross contamination during the extraction step and temperature during homogenization).
   c. Implement identity testing at upon receipt of the drug substance from
6. Process Validation:
   a. Submit the COA and analytical results for three consecutive drug substance qualification lots.
   b. Document PDR-009_00 concluded that when using a 1:1 molar ratio of B2036 primary amines to mSPA-PEG5K, the pH should be controlled at 7.65 ± 0.5. The pegylation parameters include a pH of 7.4 - 7.8, which is outside the prescribed reaction conditions. Provide a justification and supporting data for the established range.
   c. Process validation supporting the removal of PEG 4600 revealed that in-process testing of pegvisomant lots had undetectable levels reported in µg/mL. However, the method validation report from (Report VR-62.00) shows a Minimal Quantifiable Limits (MQL) range for related compounds A similar situation is also presented with the related compounds Explain this discrepancy.
   d. Submit data supporting the length of time the microbial cell paste can be held frozen.
   e. The in-process hold study used a to evaluate process intermediates. The can only separate deamidated B2036 from the main peak and cannot separate other potential degradants. In order to evaluate the effect of in-process holds, implement appropriate methods to detect potential degradants that may affect product quality. Submit the protocol and results obtained from such a study.
   f. Based on the results of the in-process hold study, the following changes are needed:
      i) Storage at 2 - 8°C of the diluted top phase. Currently it is stored at ambient temperatures; and
      ii) Storage at 2 - 8°C of the Currently the temperature is unspecified.
   g. Submit data supporting the in-process holds for the
   h. Submit the shipping validation protocol and results for the drug substance.
7. B2036 Reference Standard:
   a. Submit the specifications (tests, analytical procedures, and acceptance criteria) for qualifying the B2036 reference standard.

b. Comparative analysis between the Genentech reference material (24127-26-6) and the reference material (I1807005-B) shows a different purity level by (reduced and non-reduced). Based on the comparability analysis, these products are not comparable. Once the production process has been optimized to produce a comparable product, manufacture and fully characterize a new B2036-PEG reference standard (see ICH Q6B).

c. Include purity specifications for using.

d. Develop a method to quantitate the level of and establish a specification when qualifying the reference standard.

8. B2036-PEG Reference Standard:

a. Submit the specifications for qualifying the B2036-PEG reference standard.

b. Comparative analysis between the Genentech reference material (B2036-PEG GHA-30-1) and the reference material (GHA-FB-0698-2) shows a different purity level by. Based on the comparability analysis, these products are not comparable. Once the production process has been optimized to produce a comparable product, manufacture and fully characterize a new B2036-PEG reference standard.

c. Add analysis and establish a specification for characterizing a pegylated-B2036 reference standard.

d. Submit analysis of the current reference standard, GHA-FB-0698-2.

9. Bulk intermediate specifications:

a. The proposed identity and purity specification for (reduced and non-reduced) stained with of "Comparable to reference material; no new bands > 1.0% intensity marker" should also include analysis by silver stain along with appropriate acceptance criteria. Alternatively, (reduced and non-reduced) gels with silver stain can replace gels stained with

b. Include purity specifications for trisulfide using.

c. The purity acceptance criteria of "≤ 2% other peaks with individual impurities < 1%" is not supported by the data and should be deleted. If other peaks occur, these should be identified and characterized.

d. Revise the specifications to include the following attributes:

i) Related substance: Desamido B2036; and

ii) Impurities: N-succinyl B2036, Norleucine B2036, Trisulfide B2036, Aggregate B2036, Des-Phe, and clipped-B2036.

10. Drug substance specifications:

a. Add the following specifications to the drug substance with a footnote to indicate that testing is performed at the bulk intermediate stage:

i) Purity by

ii) DNA testing.

b. Develop specifications for the distribution of PEG-moieties on the pegylated product (i.e., B2036-PEG3, B2036-PEG4, B2036-PEG5, etc.).

c. Develop specifications for the ratio of PEG to protein. The acceptance criteria must be based on a retrospective review of lots used in the clinical studies.

d. Evaluate product comparability of the Genentech and ——— processes using chemico-physical and biological potency testing.

e. Mean potencies for formulated bulk drug substance (Lot I1812005-B) were 7.984, 5.763 and 4.404 U/mL compared to expected protein content of 10.0, 8.0 and 6.0 mg/mL. This represents percent activity ranging from 72.0 to 79.8 % for formulated bulk drug substance at different concentrations. Based on these results, the conversion is ~ 0.75 mg = 1 unit, not the expected 1 mg = 1 unit. Provide an explanation for this discrepancy.

f. Develop quantitative methods and establish specifications to detect deamidation and oxidation of B2036-PEG.

11. Final intermediate stability:

a. The data presented do not support a three-month hold time for the final intermediate based on the following:

i) Stability at the proposed –70°C storage temperature fails the final intermediate specifications by ——— at 3 months;

ii) The ——— assay did not include any acceptance criteria to assess whether the drug substance is stable. Further, this method was not validated or demonstrated to be stability-indicating;

iii) No results were presented and no acceptance criteria have been established for the ——— ——— assays;

iv) The stability results presented for the final intermediate by ——— (reduced) are not comparable to the reference material at 12 months; and

v) The reported 12-month results were compared to time zero test station instead of testing according to the bulk intermediate specifications.

b. Submit qualitative comparative analysis of ——— (reduced and non-reduced) stained with ——— Brilliant Blue and Silver stain of retain samples at time zero and 3-month test station, ———

c. Evaluate and submit data regarding the potential presence of proteases in the bulk intermediate.

12. Drug substance stability:

a. The proposed 12-month shelf-life of the drug substance did not include testing using certain stability-indicating tests. Establish specifications for oxidized and deamidated B2036-PEG and submit lot testing to support the proposed 12-month retest.

b. The method identification numbers for Appearance, Color, Clarity, ——— and Bioassay differ from the test identification described in the NDA. The use of different methods for stability studies is not acceptable.

c. The t = 0 (time zero) ——— gels for each lot are presented as the basis of comparison with the last time point gels for each temperature arm of the stability study. Stability protocol (#1) includes the acceptance criteria, which are "comparable to the reference," not to the time zero results. Explain why the results were compared to the time zero test station.

Drug product

13. The quantitative composition of 5 mg/mL pegvisomant, 7.5 mg/mL pegvisomant, and 10.0 mg/mL pegvisomant represents the amount of protein and does not include the weight contributed by the PEG moieties. The quantity should represent the sum of both protein and PEG moieties.

14. Drug Product Specifications:

a. The bioassay is capable of measuring pegvisomant biological activity with a precision of ≤ 20.4%. The acceptance criteria for the drug product should be tightened to ± 25% of the protein content.

b. DNA and Host Cell Protein may be deleted from the drug product specifications.

c. Establish specifications for deamidation and oxidized product.

d. Revise the acceptance criteria for purity and identity by ——— to "comparable to reference material; no new bands." A one percent sensitivity marker should be run on the gel to ensure sensitivity of the staining method.

15. Drug Product Stability:

a. The proposed 24-month expiry of the drug product when stored at 25°C is not supported by the data. Batch 452653A failed the ——— acceptance criteria at 24 months/25°C. Results for pH, protein content, ——— bioassay, residual moisture, LAL, sterility, and particulates were not presented for storage at 25°C for 24 months for lots 500703A and 472153A and at 18 and 24 months for lot 523153A.

b. Although the tryptic map was presented to support the oxidation and deamidation of the molecule, this test is used to determine identity. There are no quantitative acceptance criteria for deamidation or oxidation using this method.

c. Repeat the in-use stability study for reconstituted pegvisomant and photostability studies using stability-indicating methods that can detect possible oxidation and deamidation products.

16. The product certificate for the container and closure used to store the drug substance indicates that the resin has been reground and reprocessed. Describe the source of the reground material, and substantiate the suitability of reground material for this purpose.

Pharmacology/Toxicology

17. A six-month non-rodent toxicology study with daily administration of the clinical

formulation must be performed using drug product manufactured by the same facility and process as the to-be-marketed formulation. Since the drug product is covalently bonded to PEG, an additional control group with PEG-5000 (10 to 25 times human dose) is recommended.

18. Repeat the rabbit teratology study, and include at least one dose high enough to produce signs of maternal toxicity in rabbits using the to-be-marketed drug product.

Administrative

19. The language of your June 17, 1999, Debarment Certification is not acceptable. FDA regards the following wording, adapted from section 306(k)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 335a (k)(1)), as the most acceptable form of certification:

    [Name of the applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

    Use of conditional or qualifying language, such as "*to the best of its knowledge and belief*," is not satisfactory. Please submit a new Debarment Certification.

20. Four investigators [redacted] marked the box for outcome payments on the Financial Disclosure form 3455. Please explain.

21. During recent inspections of the [redacted] facilities listed in your NDA, a number of deficiencies were noted and conveyed to your suppliers by the investigator. Satisfactory inspections of all listed facilities are required before this application may be approved.

Labeling

22. Submit revised draft labeling that incorporates the following changes. In addition, further revisions may be needed following the resolution of the preceeding deficiencies (1 - 21).

Container Label

a. The route of administration, if not oral, is required to appear on the label in accordance with 21 CFR 201.100 (b)(5). A drug packaged in a container too small shall be exempt from this regulation. If space permits, we recommend the statement, "For SQ Use Only," on the front of the label.

b. Delete "1 mL" for this lyophilized powder.

c. The amount of protein does not include the weight contributed by the PEG moieties. The quantity shown on the label must represent the sum of both protein and PEG moieties. A declaration of units should also be included.

d. Submit the draft label for the diluent vial.

Carton Label

e. Relocate the statement, "Rx Only," to the front of the label to make it more prominent.

f. Increase the prominence of the statement, "For Subcutaneous Injection Only," by increasing its font size and relocating it to the center of the labeling.

g. Delete the logo that is incorporated into the proprietary name. The logo obstructs the proprietary name, Somavert.

h. The front panel should be revised to: "Package also contains single-use Sterile Water for Injection, USP."

i. The statement, "Store at 25°C (77°C); excursions permitted to 15 – 30°C" cannot be supported because the stability of the drug product has not been established when stored at 25°C.

j. Revise the statement, "See package insert for complete product information" to read "Usual Dosage: See package insert" in accordance with 21 CFR 201.55.

k. The carton also contains 10 mL of sterile water for injection; this seems to be an illogical packaging configuration based upon the use of this product. The amount of sterile water supplied should be decreased to 1 mL, since only 1 mL of sterile water is needed to reconstitute Somavert. This will prevent a patient from reconstituting Somavert with 10 ml of sterile water and from injecting a large volume of Somavert inadvertently. In addition, a patient could inject 1 mL and receive 1/10th the dose.

l. We do not recommend the use of terminal zeros; please revise "mannitol 36.0 mg" to "mannitol 36 mg."

m. See comment (b) under *Container Label*.

n. Under the section, "Each vial contains: Pegvisomant..." the strength of Somavert is shown as 10, 15, or 20 mg per vial. This represents only the amount of protein and does not include the weight contributed by the PEG moieties. The net quantity should represent the sum of both protein and PEG moieties. A declaration of units should also be included.

Package Insert

Initial draft revisions to the package insert are provided as Enclosure 1 to this letter. In addition, we note that several statements in the label are not supported by the information submitted in the NDA:

o. Description:

i) The strength of Somavert is currently shown as 10, 15, and 20 mg per vial. This represents only the amount of protein and does not include the weight contributed by the PEG moieties. The net quantity should represent the sum of both protein and PEG moieties. A declaration of units should also be included;

ii) Add a description of the numerical range of polyethylene glycol residues per protein;

iii) Add the primary amino acid sequence showing the disulfide bonds. The schematic should indicate where the amino acid substitutions occur as compared to human growth hormone. Also, the pegylation sites in the protein should be shown;

iv) Once the corrected weight of pegvisomant has been determined, add a sentence that correlates the corrected weight with the dose used in the clinical trials (e.g., The strengths of *x*, *y*, and *z* mg/vial correspond to 10, 15, and 20 mg of protein per vial, as labeled in the clinical trials);

v) Add a description of the correlation between protein content and potency; and

vi) Add a brief description of the potency assay.

p. Dosage and Administration:

i) The statement, "SOMAVERT should be administered within two hours after reconstitution" is not supported by the reconstitution study;

ii) The strength of Somavert is currently shown as 10, 15, and 20 mg per vial. This represents only the amount of protein and does not include the weight contributed by the PEG moieties. The net quantity should represent the sum of both protein and PEG moieties. A declaration of units should also be included; and

iii) Reconstitution directions were described, but the strength of the final dosage solution in milligrams of pegvisomant per mL of reconstituted solution was not provided.

q. How Supplied:

i) Since the Sterile Water for Injection, USP, is supplied as a single dose, the diluent should be supplied in a 1 mL vial.

r. Storage:

i) The statement, "Prior to reconstitution, SOMAVERT should be stored at 25°C (77°C); excursions permitted to 15 – 30°C," cannot be supported because the stability of the drug product has not been established when stored at 25°C; and

ii) The statement, "After reconstitution, SOMAVERT should be administered within 2 hours," cannot be supported because certain stability tests were not included in the analysis.

Patient Package Insert (PPI)

s. The PPI should include information about how to pronounce the product name, what the product is used for, who should not use it, and what to avoid (if anything) while taking it. It should be put in the format we are using for all new PPIs, which follows the Medication Guide format (21 CFR 208.20). The PPI should contain a final paragraph, standard in new PPIs, about not sharing the product, using it only for the condition for which it was prescribed, and how to get more information, including availability of the Package Insert. The short text presented in the PPI prior to the instructions for use needs to be revised in accordance with the format suggested, and the language should be simplified before we can comment. Revisions to the Instructions for Use section are provided as Enclosure 2.

If additional information relating to the safety or effectiveness of this drug becomes available, revision

of the labeling may be required.

While not required prior to approval, we have the following comments and requests for information that should be addressed:

Pharmacology/Toxicology

1. A two-year rodent carcinogenicity study should be conducted. Submit your plans for this study to include dates for submission of the final protocol, initiation of the study, completion of the study, and submission of the final report. We recommend you submit the protocol for review by our Executive Carcinogenicity Assessment Committee prior to initiation of the study. Additional carcinogenicity testing for this indication may not be needed pending a negative outcome of a valid study.

Clinical Pharmacology & Biopharmaceutics

2. There is uncertainty as to the cross-reactivity of impurities in the drug product when using the RIA for detection of pegvisomant concentrations in serum. It is possible that some of these impurities are bioactive. Purify these impurities, and evaluate their cross-reactivity with the RIA as well as their bioactivity. Together, these procedures will contribute to the understanding of the active components of pegvisomant.
3. Data show an interaction between octreotide and cyclosporin which may be growth hormone mediated. Since pegvisomant can cause an apparent decrease in growth hormone by blocking receptors, you should conduct an *in vivo* drug interaction study to address any potential pharmacokinetic interaction between pegvisomant and cyclosporin.
4. No data were submitted on the route of elimination of pegvisomant in humans. Provide data showing the route of elimination and/or metabolic pathways of pegvisomant. These data may be the basis for future recommendations of pharmacokinetic studies in special populations (e.g., hepatic and/or renal impairment).
5. To further understand the metabolic effects that pegvisomant may have on other drugs, conduct in vitro metabolism/drug interaction studies as per the guidance, "Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro" (http://www.fda.gov/cder/guidance/clin3.pdf).

Clinical

6. Establish a registry of acromegalic patients treated with pegvisomant in order to better monitor the rate of spontaneous reporting of liver test (LT) abnormalities during the initial marketing of pegvisomant.
7. Obtain additional immunogenicity data (including anti-pegvisomant antibodies*, anti-growth hormone (GH) antibodies, and anti-host cell protein antibodies) when the purity of the to-be-marketed product has improved to an acceptable level.

**Development of a validated assay for anti-pegvisomant antibodies which can be performed*

in the presence of therapeutic serum levels of pegvisomant should be undertaken.

8. Consider a three-armed trial comparing the efficacy (e.g., percent reduction in IGF-I levels) of pegvisomant without a loading dose and after loading doses of 40 and 80 mg.
9. Consider a long-term study of the durability of pegvisomant efficacy.
10. Consider a study comparing the efficacy of pegvisomant and somatostatin analogue (SA) therapy (the primary medical therapy for acromegaly currently available).
11. Consider a study exploring the utility of adding SA therapy to pegvisomant therapy in patients with clinically and biochemically resistant acromegaly with or without evidence of progressive growth of the underlying GH-secreting pituitary adenoma.
12. Pending approval of this NDA, the following parameters should be monitored prior to the initiation or reinitiation of pegvisomant therapy in patients continuing to receive pegvisomant in clinical trials and subsequently at appropriate intervals. Refer to Enclosure 1 (Package Insert) for further discussion:
    a. LTs
    b. Renal function
    c. IGF-I levels
    d. GH levels
    e. MRI scans of the sella turcica
    f. Incidence of hypoglycemic reactions, and decrease in requirement for anti-diabetic medications (e.g., oral hypoglycemics, insulin) in acromegalics with diabetes mellitus.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
    a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
    b. Present tabulations of the new safety data combined with the original NDA data.
    c. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    d. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division of Metabolic and Endocrine Drug Products to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Crystal King, P.D., M.G.A., Regulatory Project Manager, at (301) 827-6423.

Sincerely yours,

{See appended electronic signature page}

John K. Jenkins, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure 1: Package Insert
Enclosure 2: Patient Package Insert

/S/

1/26/01
See DFS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Jenkins
6/26/01 04:16:25 PM

19 page(s) of revised draft labeling has been redacted from this portion of the review.